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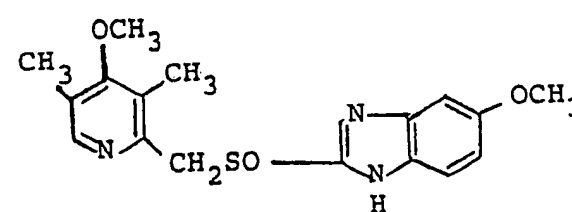
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : C07D 401/12, A61K 31/44	A1	(11) International Publication Number: WO 89/ 03829 (43) International Publication Date: 5 May 1989 (05.05.89)
(21) International Application Number: PCT/SE88/00573 (22) International Filing Date: 27 October 1988 (27.10.88) (31) Priority Application Numbers: 8704247-9 8704436-8 (32) Priority Dates: 30 October 1987 (30.10.87) 13 November 1987 (13.11.87) (33) Priority Country: SE (71) Applicant (for all designated States except US): AK-TIEBOLAGET HÄSSLE [SE/SE]; S-431 83 Mölndal (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : LINDERG, Per [SE/SE]; Knapeshall 64, S-436 00 Askim (SE). WALL-MARK, Björn [SE/SE]; Råda Portar, S-435 00 Mölnlycke (SE). VÄÄNÄNEN, Kalervo [FI/FI]; Peikontie 2D43, SF-90550 Oulu (FI). HÄKANSON, Rolf [SE/SE]; Tunnbindargatan 8, S-222 36 Lund (SE).		(74) Agents: MIKSCHKE, Gerhard et al.; AB Astra, Patent and Trademark Department, S-151 85 Södertälje (SE). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BR, CH, CH (European patent), DE, DE (European patent), DK, FI, FR (European patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: OMEPRAZOLE FOR TREATMENT OF DISEASES RELATED TO BONE LOSS <div style="text-align: center;">  </div> <div style="text-align: right;"> (I) </div> (57) Abstract <p>A method for the treatment of osteoporosis, Paget's disease of bone, hyperparathyroidism, malignant neoplasms causing hypercalcaemia, parodontal diseases and implant-related bone loss comprising administration to a patient suffering therefrom an amount of a compound of formula (I), or a prodrug or a pharmaceutically acceptable salt thereof.</p>		

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Omeprazole for treatment of diseases related to bone loss.

Field of the Invention

The present invention is related to a novel method for the treatment of several bone affecting diseases, especially osteoporosis, which are characterized by loss of bone mass.

Background of the Invention

The balance in normal subjects between, on one hand, bone formation, which is associated with the number and activity of osteoblasts, that is cells associated with the production of bone in the organism, and on the other hand, bone loss which is associated with the number and activity of osteoclasts, that is cells associated with the absorption and removal of bone, is disturbed in several bone affecting diseases. At the present time there is no good treatment for any of these diseases, among which can be mentioned osteoporosis, Paget's disease of bone, hyperparathyroidism and related disorders, and several malignant neoplasms where tumor cells are producing osteoclast-activating factors and cause hypercalcemia.

Worldwide the most urgent need is for the treatment of osteoporosis and tumor associated hypercalcemia. In some areas, e.g. in England and in some other parts of Europe there is also high incidence of Paget's disease of bone.

In osteoporosis bone formation as well as bone resorption are disturbed, resulting in loss of bone tissue, decreased bone mass, and bone fragility. Osteoporosis predominantly affects the elderly, but also other groups such as postmenopausal

women, where an estrogen deficit is believed to be a significant etiological factor, and immobilized patients. At this point it is not possible to clear up the whole picture of the disease mechanism and estimate which is the primary cause of osteoporosis. However, about 25% of the osteoporotic females belong to what is called "rapid bone losers" and at least in those patients the bone resorption rate is probably increased. Landry and Fleisch showed in immobilization induced osteoporosis that bone resorption rate was accelerated, (Landry, M. and Fleisch, H.: The influence of immobilization on bone formation as evaluated the incorporation of tetracyclines. J. Bone Joint Surg. 46B:764, 1964).

The clinical manifestations of osteoporosis comprise fractures, especially hip fractures, but also vertebral fractures and fractures of the proximal radius, and complication of such fractures.

In Finland it has been estimated that about 10% of all surgical hospital beds are used for the treatment of osteoporosis related fractures (Lüthje, P.: Reisiluunkaulan ja trokanterin murtumapotilaiden hoito ja ennuste sekä hiondon kustannukset. Thesis. Helsinki 1983).

The present methods for the treatment of osteoporosis include exercise; administration of estrogen, especially for postmenopausal women; and consumption of calcium or calcium containing material such as milk. Calcitonin, a hormone associated with calcium metabolism, has also been used in the treatment of osteoporosis.

Several malignant tumors are known to be associated by hypercalcemia which is due to increased osteoclastic activity.

This is a common complication for instance in the case of breast cancer and prostate cancer which are both one of the most common malignant tumors. Hypercalcemia is due to both systemic and local factors. Some malignant cells are known to secrete agents which stimulate bone resorption (Sato, K., Fujii, Y., Kachivehi, T., Kasono, K., Shizume, K.: Production of interleukin 1 alpha (IL-1 α)-like activity and colony stimulating activity by clonal squamous cell carcinomas derived from patients with hypercalcemia and leucocytosis. In: Calcium Regulation and Bone Metabolism Vol. 9 (eds. D.V. Cohn, T.J. Martin, P.J. Meunier), 1986).

In malignant hypercalcemia calcitonin and diphosphonate treatment has been used.

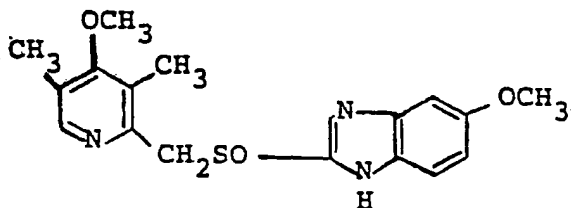
Paget's disease (or osteitis deformans) of bone is a disease of unknown etiology where bone resorption and remodelling are increased leading sometimes even to the fractures of affected bone. Bone pain is the main indication of treatment in these patients. In these patients there is highly elevated local osteoclastic bone destruction. The incidence of osteitis deformans is very low in Scandinavian countries. In England it has been estimated to be present in 3-4% of the population on the basis of autopsy studies (Anderson's Textbook of Pathology 1986). It is very rare in patients under 40 years. Calcitonin and diphosphonates are also used in the treatment of Paget's disease.

Other disease states for the treatment of which antagonists to osteoclastic activity might be useful, are parodontal diseases and prosthetic and implant bone losses.

It is an object of the present invention to provide compounds which by affecting the balance between osteoblast and osteoclast activity can be useful for prophylactic and therapeutic treatment of diseases as indicated above which are associated with bone loss. It is believed that the use of these compounds will also ultimately result in an increase of the bone mass.

Outline of the invention

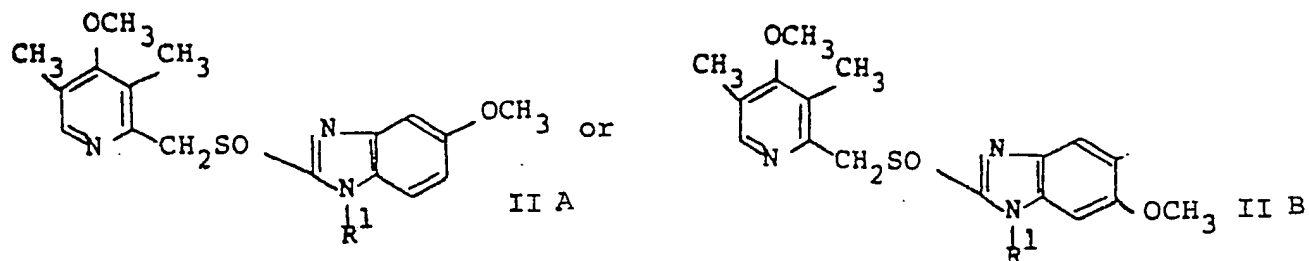
According to the present invention it has been found that the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, of the formula



I

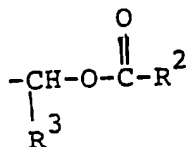
or a prodrug or a therapeutically acceptable salt thereof, is useful in the prophylactic and therapeutic treatment of osteoporosis; Paget's disease of bone; hyperparathyroidism, both primary and secondary; malignant neoplasms where tumor cells are producing osteoclast-activity factors and cause hypercalcinemia; immobilization-induced osteoporosis; parodontal diseases; and prosthetic and implant-related bone losses. Examples of pharmaceutically acceptable salts are alkali salts such as sodium and potassium salts, and calcium and magnesium salts.

The term "prodrug" is intended to cover compounds which after administration to the patient, are converted to a compound of the formula I. More particularly, examples of prodrug of compounds the formula I are of the formula



where the radical R^1 is selected from

(A)



wherein

R^3 is (a) H

(b) alkyl containing 1-4 carbon atoms

R^2 is (a) alkyl containing 1-6 carbon atoms

(b) cycloalkyl containing 3-7 carbon atoms

(c) alkoxy containing 1-6 carbon atoms

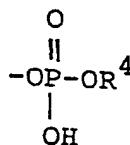
(d) aryl

(e) aryl, optionally substituted with alkyl containing 1-4 carbon atoms, alkoxy containing 1-4 carbon atoms, halogen, CF_3 , alkanoyl containing 2-5 carbon atoms, or alkoxycarbonyl containing 2-5 carbon atoms.

- (f) aryloxy, optionally substituted with alkyl containing 1-4 carbon atoms, alkoxy containing 1-4 carbon atoms, halogen, CF_3 , alkanoyl containing 2-5 carbon atoms, or alkoxycarbonyl containing 2-5 carbon atoms.
- (g) arylalkoxy containing 1-6 carbon atoms in the alkoxy part, wherein the aryl part optionally is substituted with alkyl containing 1-6 carbon atoms and/or alkoxy containing 1-6 carbon atoms

and

(B)



wherein

R^4 is (a) H

(b) alkyl containing 1-6 carbon atoms

Illustrative examples of the various radicals in the formula II are as follows. These illustrative examples will be applicable to the different radicals depending on the number of carbon atoms prescribed for each radical.

The group alkyl in the definitions of R^2 , R^3 and R^4 is exemplified by methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl,

cyclopentylethyl, and cyclohexylmethyl. Lower alkyl groups containing 1-4 carbon atoms are especially preferred.

The group alkoxy in the definitions of R^2 is exemplified by methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentoxy, i-pentoxy, n-hexoxy, cyclopropoxy, cyclopentoxy, cyclohexoxy, cyclopropylmethoxy, cyclopentylmethoxy, cyclopentylethoxy, and cyclohexylmethoxy. Lower alkoxy groups are preferred, especially those containing 1-4 carbon atoms, preferably a lower alkoxy group having especially preferred 1-3 carbon atoms, e.g. methoxy, ethoxy, n-propoxy or isopropoxy.

Halogen in the definitions of R^2 , is chloro, bromo, fluoro and iodo, preferably chloro, bromo, and fluoro.

The group aryl when present in R^2 has preferably up to 10 carbon atoms, especially preferred up to 6 carbon atoms, e.g. a phenyl group.

R^2 , representing an aryloxy group has preferably up to 10 carbon atoms, especially preferred up to 6 carbon atoms, e.g. a phenoxy group.

Alkanoyl in R^2 contains from 2 to 6 carbon atoms and is preferably HCO , CH_3CO , CH_3CH_2CO , $CH_3(CH_2)_2CO$, or $HC(CH_3)_2CO$.

Alkoxycarbonyl in R^2 contains an alkoxy group as illustrated under "alkoxy" above.

Accordingly, the invention relates to

- a method for the prophylactic and therapeutic treatment of each of the ailments above by administering to a host in need thereof of a therapeutically effective amount of a compound of the formula I, or a prodrug or a therapeutically acceptable salt thereof
- a pharmaceutical preparation for use in the prophylactic and therapeutic treatment of each of the ailments above comprising a compound of the formula I as active ingredient, or a prodrug or a therapeutically acceptable salt thereof
- a compound of the formula I or a prodrug or a therapeutically acceptable salt thereof for use in the manufacture of a medicament for the prophylactic and therapeutic treatment of each of the ailments above.
- a method for improving the healing rate of bone fractures by administering to a host in need thereof of an effective amount of a compound of the formula I.

Pharmacological tests

Sprague-Dawley male rats (Alab, Stockholm, Sweden) weighing 175-200 g before the tests were used. They obtained a standard diet consisting of rat feed pellets (Alab, Stockholm, Sweden) and tap water.

Ten rats were given omeprazole (Hässle, Sweden), 400 $\mu\text{mol/kg}$ body weight, once daily orally during 26 days. Twelve rats were used as untreated controls.

^{45}Ca incorporation into the skeleton

2×10^6 cpm $^{45}\text{CaCl}_2$ (Radiochemical Center, Amersham, England) were administered orally by ventricular sond. The rats were killed by tapping blood via abdominal aorta 4 hours after the peroral administration of ^{45}Ca . Radius, sternum, tibia and femur were removed by dissection. Radius and sternum were cleaned, weighed and placed in an oven at 800°C during 24 hours. The ashes were weighed and dissolved in 1M HCl. 10 ml Picofluor-40 (Packard) was added, whereafter the tubes were closed and shaken vigourosly before counting in a Beckman B-counter.

Radioimmunoanalysis of gastrin

Serum was prepared at the blood tapping from each rat and gastrin was determined by radioimmunoanalysis (Stadil, F. & Rehfeld, J.F. (1973) Determination of gstrin in serum. An evaluation of the reliability of a radioimmunossay, Scan. J. Gastroent. 8, 101-112; Håkanson, R., Kroesen, J.H., Liedberg, G., Oscarson, J., Rehfeld, J.E. & Stadil, F. (1974) Correlation between serum gastrin concentration and rat stomach histidine decarboxylase activity, J. Physiol. 243, 483-498).

Operations were performed under ether anaesthesia. Fundectomy,

comprising resection of the acid producing part of the ventricle, was performed as has been described in detail by Alumets et al (Alumets, J., El Munshid, H.A., Håkanson, R., Hedenbro, J., Liedberg, G., Oscarson, J., Rehfeld, J.F., Sundler, F. and Vallgren, S., Gastrin cell proliferation after chronic stimulation. Effects of vagal denervation or gastric surgery in the rat. J. Physiol. 298, 557-569 (1980)). Gastrectomia was prepared by resection of the stomach followed by suturation of esophagus and duodenum end to end. Operated animals were allowed to recover for one week before treatment with omeprazole, as has been described in "Pharmacological tests".

The test results are given in Fig. 1 and Fig. 2.

Description of the drawings

Fig. 1 shows the concentration of gastrin expressed as picogram/ml serum with untreated control rats (average of 12 rats respectively average of 7 rats) and with omeprazole-treated rats (average of 10 rats) after treatment for 26 days. Fig. 2 shows the amount of radioactive calcium which has been incorporated into the skeleton (radius respectively sternum) expressed in cpm/mg bone ashes. A shows the average of 12 control rats, B shows the average of 10 omeprazole-treated rats, C shows the average of 12 control rats, D shows the average of 10 omeprazole-treated rats.

The continuous lines represent the average of given number of rats and the dashed lines represent the standard error of the average value. The stars designate the significance (i.e. the difference between control and test substance according to Student's t-test $p < 0.05 = x$; $p < 0.01 = xx$ and $p < 0.005 = xxx$).

Results

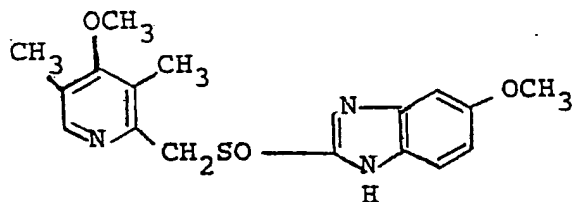
Omeprazole-treated rats and fundectomized rats developed pronounced and constant hypergastrinemia, which is seen in the attached Fig. 1. The hypergastrinemia which had been developed by treatment with omeprazole-stimulated ^{45}Ca -incorporation into the skeleton, which is seen in the attached Fig. 2.

Hypergastrinemia caused by fundectomy did not stimulate ^{45}Ca -incorporation into the skeleton. Neither did omeprazole-treatment in gastrectomized rats stimulate ^{45}Ca -incorporation into the skeleton.

The tests given above showed clearly that treatment with omeprazole led to increased incorporation of calcium into the skeleton. This may be due to hypergastrinemia which in turn via some factor in the acid-producing part of the stomach seems to control the incorporation of calcium into skeleton.

CLAIMS

1. A method for the treatment of osteoporosis by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I below (Omeprazole), or a prodrug or a therapeutically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier:



I

2. A method for the treatment of Paget's disease of bone by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.
3. A method for the treatment of primary and secondary hyperparathyroidism by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.

4. A method for the treatment of such malignant neoplasms where tumor cells are producing osteoclast-activating factors, by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.
5. A method for the treatment of parodontal diseases, by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.
6. A method for the treatment of prosthetic and implant-related bone loss, by administering to a host in need of such treatment of a therapeutically effective amount of a compound of the formula I as defined in claim 1, optionally together with a pharmaceutically acceptable carrier.
7. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of osteoporosis.
8. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of Paget's disease of bone.
9. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of primary and secondary hyperparathyroidism.

10. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of such malignant neoplasms where tumor cells are producing osteoclast activating factors.
11. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of parodontal diseases.
12. A compound of the formula I as defined in claim 1 for use in the manufacture of a medicament for the treatment of prosthetic and implant-related bone loss.
13. A pharmaceutical preparation for use in the treatment of osteoporosis; Paget's disease of bone; primary and secondary hyperparathyroidism; such malignant neoplasms where tumor cells are producing osteoclast-activating factors; such parodontal diseases which are associated with bone loss; or prosthetic and implant-related bone loss; and comprising a compound of the formula I as defined in claim 1 as active ingredient.
14. A method for improving the healing rate of bone fractures by administering to a host in need thereof an effective amount of a compound of the formula I as defined in claim 1.
15. A compound as defined in claim 1 for use in the manufacture of a medicament for improving the healing rate of bone fractures.

16. A pharmaceutical preparation for use in improving the healing rate of bone fractures, comprising a compound of the formula I as defined in claim 1 as active ingredient.

Fig.1

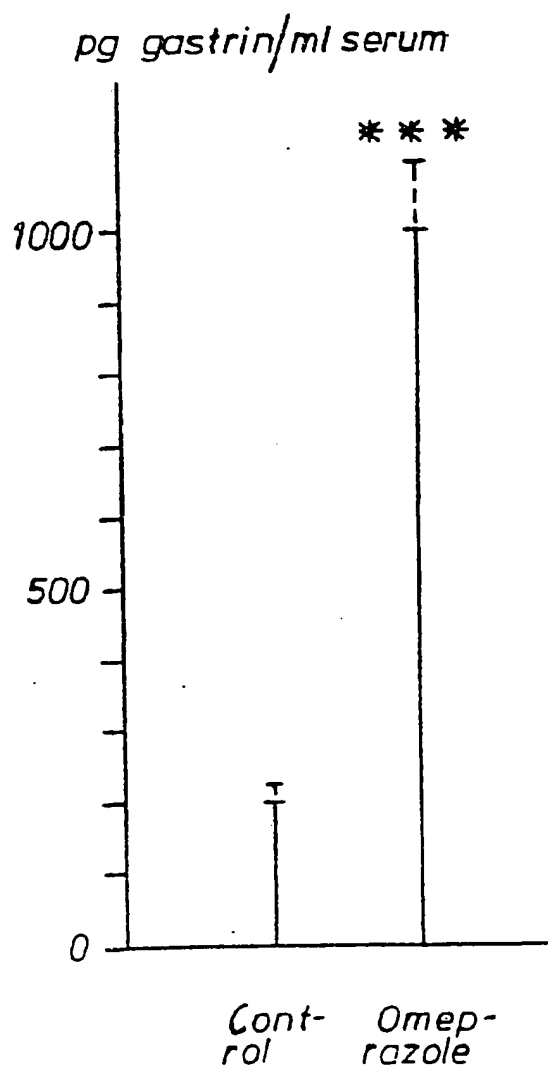
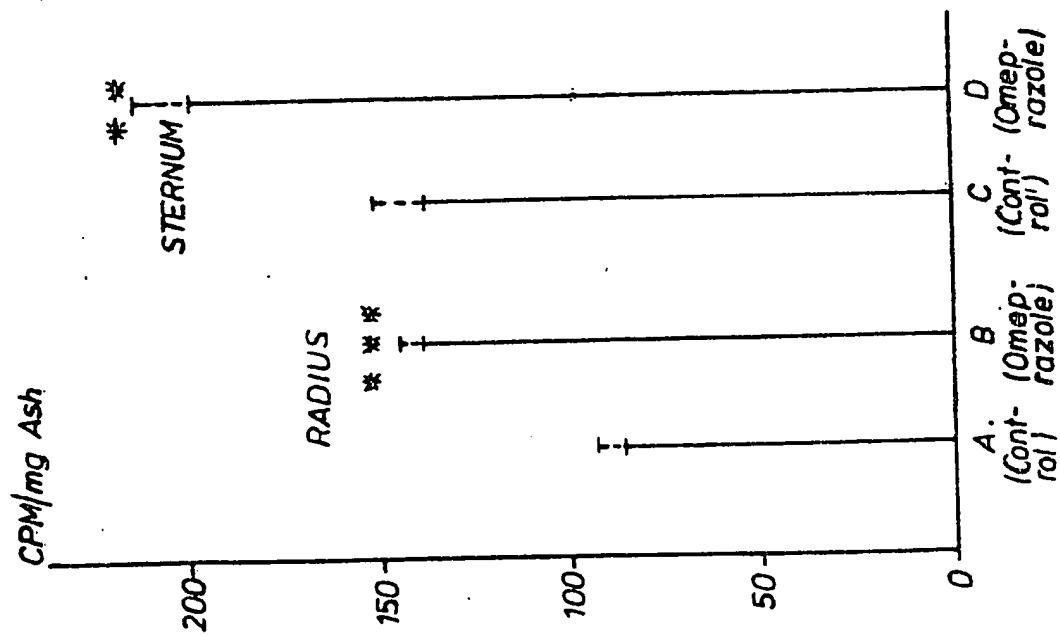


Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No PCT/SE88/00573

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC 4 <div style="border: 1px solid black; padding: 2px; margin-top: 5px;">C 07 D 401/12, A 61 K 31/44</div>											
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black; font-size: small;">Classification System</th> <th style="border-bottom: 1px solid black; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">IPC 4</td> <td style="padding: 5px;">C 07 D 401/12; A 61 K 31/44</td> </tr> <tr> <td style="padding: 5px;">US C1</td> <td style="padding: 5px;">424:263; 514:295; 546:271</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div> <div style="padding: 10px; margin-top: 10px;">SE, NO, DK, FI classes as above</div>			Classification System	Classification Symbols	IPC 4	C 07 D 401/12; A 61 K 31/44	US C1	424:263; 514:295; 546:271			
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US C1	424:263; 514:295; 546:271										
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: x-small;">Category ⁹</th> <th style="width: 70%; font-size: x-small;">Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; font-size: x-small;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">Calcified Tissue International, Vol. 38, 1986, J. Tuukkanen & H.K. Väänänen, "Omeprazole, a specific inhibitor of H⁺-K⁺-ATPase, inhibits bone resorption in vitro", pages 123-125.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7-13, 15-16</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">S. Yousuf Ali, "Cell mediated calcification and matrix vesicles. Proceedings of the IV International conference on matrix vesicles, Cambridge, 1-5 July 1985", publ. 1986, by Excerpta Medica (Amsterdam), pages 143-146.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7-13, 15-16</td> </tr> </tbody> </table>			Category ⁹	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	Calcified Tissue International, Vol. 38, 1986, J. Tuukkanen & H.K. Väänänen, "Omeprazole, a specific inhibitor of H ⁺ -K ⁺ -ATPase, inhibits bone resorption in vitro", pages 123-125.	7-13, 15-16	X	S. Yousuf Ali, "Cell mediated calcification and matrix vesicles. Proceedings of the IV International conference on matrix vesicles, Cambridge, 1-5 July 1985", publ. 1986, by Excerpta Medica (Amsterdam), pages 143-146.	7-13, 15-16
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<div style="font-size: x-small;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div>											
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of the Actual Completion of the international Search <div style="text-align: center; margin-top: 5px;">1989-01-23</div> </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 5px;">1989-01-27</div> </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center; margin-top: 5px;">Swedish Patent Office</div> </td> <td style="border-bottom: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; margin-top: 5px;"> Göran Karlsson </div> </td> </tr> </table>			Date of the Actual Completion of the international Search <div style="text-align: center; margin-top: 5px;">1989-01-23</div>	Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 5px;">1989-01-27</div>	International Searching Authority <div style="text-align: center; margin-top: 5px;">Swedish Patent Office</div>	Signature of Authorized Officer <div style="text-align: center; margin-top: 5px;"> Göran Karlsson </div>					
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-6, 14 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy.

2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.